Claims

1. A method for shunting toxic substances, present in a brain ventricle, to the sinus system of an individual suffering from, or at risk of developing, a condition related to the retention and/or accumulation of toxic substances in brain tissue and/or the CSF space, said method comprising the steps of

   i) providing a shunt system for shunting cerebrospinal fluids comprising toxic substances, such as amyloid proteins, from a brain ventricle to the sinus system of an individual, wherein said shunt system comprises

      a) a shunt body allowing fluid communication between a brain ventricle and a part of the sinus system of the individual,

         wherein said shunt body comprises a flow restricting component capable of maintaining a passive and essentially constant resistance to flow of cerebrospinal fluids through the shunt body,

      b) a brain ventricle catheter capable of being connected to the shunt body at a first location thereof,

         wherein the brain ventricle catheter is capable of draining cerebrospinal fluids from a brain ventricle to the shunt body, and

      c) a sinus catheter capable of being connected to the shunt body at a second location thereof,

         wherein the sinus catheter is capable of draining to the sinus system of the individual cerebrospinal fluids having been drained from a brain ventricle and passed through the flow restricting component of the shunt body to the sinus catheter,

         wherein optionally either all or part of i) the internal or external surface of the shunt body, or either all or part of ii) the internal or external surface of the brain ventricle catheter, or either all or part of iii)

the internal or external surface of the sinus catheter, can comprise a biocompatible/hemocompatible material comprising an inert surface preventing biological material from maintaining contact with the inert surface, and/or comprising a hemocompatible surface coated with a plurality of charged species capable of increasing the hemocompatibility of the surface,

ii) inserting into a brain ventricle of the individual the brain ventricle catheter of the shunt system capable of being connected to the shunt body at a first location thereof,

iii) inserting into the sinus system of the individual the sinus catheter of the shunt system capable of being connected to the shunt body at a second location thereof, and

iv) shunting toxic substances, such as amyloid proteins, present in a brain ventricle to the sinus system of the individual suffering from, or at risk of developing, a condition related to the retention and/or accumulation of toxic substances in brain tissue and/or the CSF space.

2. The method of claim 1, wherein the condition related to the retention and/or accumulation of toxic substances in the CSF is Alzheimer's disease.

3. The method of any of the previous claims, wherein the condition related to the retention and/or accumulation of toxic substances in the CSF is Down's Syndrome.

4. The method of any of the previous claims, wherein the condition related to the retention and/or accumulation of toxic substances in the CSF is hereditary cerebral hemorrhage with amyloidosis of the Dutch-Type (HCHWA-D) or the like.

5. The method of any of the previous claims, wherein the condition related to the retention and/or accumulation of toxic substances in the CSF is epilepsy.

6. The method of any of the previous claims, wherein the condition related to the retention and/or accumulation of toxic substances in the CSF is Parkinson's disease.

7. The method of any of the previous claims, wherein the condition related to the retention and/or accumulation of toxic substances in the CSF is a polyneuropathy.

8. The method of any of the previous claims, wherein the condition related to the retention and/or accumulation of toxic substances in the CSF is selected from one or more of multiple sclerosis, amyotrophic lateral sclerosis (ALS), myasthenia gravis, muscular dystrophy, dystrophy myotonic or another myotonic syndrome, polymyositis, dermatomyositis, a brain tumor or Guillain-Barre-Syndrome.

9. The method of any of claims 1-8, wherein the toxic substance is one or more of tau, beta-2 microglobulin or A-beta-42

10. The method of any of claims 1-9, wherein the flow restricting component of the shunt body is capable of maintaining a passive and essentially constant resistance to flow of cerebrospinal fluids through the shunt body of a constant value of from 0.1 to less than 8 mm Hg/ml/min.

11. The method of any of claims 1-9, wherein the flow restricting component of the shunt body is capable of maintaining a passive and essentially constant resistance to flow of cerebrospinal fluids through the shunt body of a constant value of from 0.5 to less than 8 mm Hg/ml/min.

12. The method of any of claims 1-9, wherein the flow restricting component of the shunt body is capable of maintaining a passive and essentially constant resistance to flow of cerebrospinal fluids through the shunt body of a constant value of from 1 to less than 8 mm Hg/ml/min.

13. The method of any of claims 1-9, wherein the flow restricting component of the shunt body is capable of maintaining a passive and essentially constant resis-

tance to flow of cerebrospinal fluids through the shunt body of a constant value of from 2 to less than 8 mm Hg/ml/min.

14. The method of any of claims 1-9, wherein the flow restricting component of the shunt body is capable of maintaining a passive and essentially constant resistance to flow of cerebrospinal fluids through the shunt body of a constant value of from 3 to less than 8 mm Hg/ml/min.

15. The method of any of claims 1-9, wherein the flow restricting component of the shunt body is capable of maintaining a passive and essentially constant resistance to flow of cerebrospinal fluids through the shunt body of a constant value of from 4 to less than 8 mm Hg/ml/min.

16. The method of any of claims 1-9, wherein the flow restricting component of the shunt body is capable of maintaining a passive and essentially constant resistance to flow of cerebrospinal fluids through the shunt body of a constant value of from 6 to less than 8 mm Hg/ml/min.

17. The method of any of claims 1-9, wherein the flow restricting component of the shunt body is capable of maintaining a passive and essentially constant resistance to flow of cerebrospinal fluids through the shunt body of a constant value of from 0.1 to 7 mm Hg/ml/min.

18. The method of any of claims 1-9, wherein the flow restricting component of the shunt body is capable of maintaining a passive and essentially constant resistance to flow of cerebrospinal fluids through the shunt body of a constant value of from 0.1 to 6 mm Hg/ml/min.

19. The method of any of claims 1-9, wherein the flow restricting component of the shunt body is capable of maintaining a passive and essentially constant resistance to flow of cerebrospinal fluids through the shunt body of a constant value of from 0.1 to 5 mm Hg/ml/min.

20. The method of any of claims 1-9, wherein the flow restricting component of the shunt body is capable of maintaining a passive and essentially constant resis-

tance to flow of cerebrospinal fluids through the shunt body of a constant value of from 0.1 to 4 mm Hg/ml/min.

21. The method of any of claims 1-9, wherein the flow restricting component of the shunt body is capable of maintaining a passive and essentially constant resistance to flow of cerebrospinal fluids through the shunt body of a constant value of from 0.1 to 3 mm Hg/ml/min.

22. The method of claim 1, wherein the flow restricting component of the shunt body is capable of maintaining a passive and essentially constant resistance to flow of cerebrospinal fluids through the shunt body of a constant value of from 0.1 to 2 mm Hg/ml/min.

23. The method of any of claims 1-9, wherein the flow restricting component of the shunt body is capable of maintaining a passive and essentially constant resistance to flow of cerebrospinal fluids through the shunt body of a constant value of from 0.1 to 1 mm Hg/ml/min.

24. The method of any of claims 1-9, wherein the flow restricting component of the shunt body is capable of maintaining a passive and essentially constant resistance to flow of cerebrospinal fluids through the shunt body of a constant value of from 1 to 7 mm Hg/ml/min.

25. The method of any of claims 1-9, wherein the flow restricting component of the shunt body is capable of maintaining a passive and essentially constant resistance to flow of cerebrospinal fluids through the shunt body of a constant value of from 1 to 5 mm Hg/ml/min.

26. The method of any of claims 1-9, wherein the flow restricting component of the shunt body is capable of maintaining a passive and essentially constant resistance to flow of cerebrospinal fluids through the shunt body of a constant value of from 1 to 3 mm Hg/ml/min.

27. The method of any of claims 1-9, wherein the flow restricting component of the shunt body is capable of maintaining a passive and essentially constant resis-

tance to flow of cerebrospinal fluids through the shunt body of a constant value of from 1 to 2 mm Hg/ml/min.

28. The method of any of claims 1-9, wherein the flow restricting component of the shunt body is capable of maintaining a passive and essentially constant resistance to flow of cerebrospinal fluids through the shunt body of a constant value of from 2 to 7 mm Hg/ml/min.

29. The method of any of claims 1-9, wherein the flow restricting component of the shunt body is capable of maintaining a passive and essentially constant resistance to flow of cerebrospinal fluids through the shunt body of a constant value of from 2 to 6 mm Hg/ml/min.

30. The method of any of claims 1-9, wherein the flow restricting component of the shunt body is capable of maintaining a passive and essentially constant resistance to flow of cerebrospinal fluids through the shunt body of a constant value of from 2 to 5 mm Hg/ml/min.

31. The method of any of claims 1-9, wherein the flow restricting component of the shunt body is capable of maintaining a passive and essentially constant resistance to flow of cerebrospinal fluids through the shunt body of a constant value of from 1 to 4 mm Hg/ml/min.

32. The method of any of claims 1-9, wherein the flow restricting component of the shunt body is capable of maintaining a passive and essentially constant resistance to flow of cerebrospinal fluids through the shunt body of a constant value of from 4 to less than 8 mm Hg/ml/min.

33. The method of any of claims 1-9, wherein the flow restricting component of the shunt body is capable of maintaining a passive and essentially constant resistance to flow of cerebrospinal fluids through the shunt body of a constant value of from 0.1 to 0.5 mm Hg/ml/min, such as from 0.5 to 1.0 mm Hg/ml/min, for example from 1.0 to 1.5 mm Hg/ml/min, such as from 1.5 to 2.0 mm Hg/ml/min, for example from 2.0 to 2.5 mm Hg/ml/min, such as from 2.5 to 3.0 mm Hg/ml/min, for example from 3.0 to 3.5 mm Hg/ml/min, such as from 3.5 to 4.0 mm

Hg/ml/min, for example from 4.0 to 4.5 mm Hg/ml/min, such as from 4.5 to 5.0 mm Hg/ml/min, for example from 5.0 to 5.5 mm Hg/ml/min, such as from 5.5 to 6.0 mm Hg/ml/min, for example from 6.0 to 6.5 mm Hg/ml/min, such as from 6.5 to 7.0 mm Hg/ml/min, for example from 7.0 to 7.5 mm Hg/ml/min, such as from 7.5 to less than 8.0 mm Hg/ml/min, for example from 0.1 to 1 mm Hg/ml/min, such as from 1 to 2 mm Hg/ml/min, for example from 2 to 3 mm Hg/ml/min, such as from 3 to 4 mm Hg/ml/min, for example from 4 to 5 mm Hg/ml/min, such as from 5 to 6 mm Hg/ml/min, for example from 6 to 7 mm Hg/ml/min, such as from 7 to less than 8 mm Hg/ml/min, for example from 0.1 to 2 mm Hg/ml/min, such as from 2 to 4 mm Hg/ml/min, for example from 4 to 6 mm Hg/ml/min, such as from 6 to less than 8 mm Hg/ml/min, for example from 0.1 to 2.5 mm Hg/ml/min, such as from 2.5 to 5.0 mm Hg/ml/min, for example from 5.0 to 7.5 mm Hg/ml/min, such as from 3.0 to 7.0 mm Hg/ml/min, for example from 3.5 to 6.5 mm Hg/ml/min, such as from 4.0 to 6.0 mm Hg/ml/min, for example from 4.5 to 5.5 mm Hg/ml/min, such as about 5.0 mm Hg/ml/min.

34. The method of any of claims 1 to 33 wherein the flow restricting component of the shunt body is selected from the group consisting of a tubular structure, a plurality of tubular structures, a porous mass, a fibrous mass, a structure being restricted by co-extending fibres arranged therein, and a structure being restricted by co-extending rods arranged therein.

35. The method of any of claims 1 to 33 wherein the flow restricting component of the shunt body comprises at least one tubular structure having an internal radius of more than 0.05 mm and preferably less than 0.50 mm, for example a tubular structure having an internal radius of about 0.06 mm, for example about 0.07 mm, such as about 0.08 mm, for example about 0.09 mm, such as about 0.10 mm, for example about 0.11 mm, such as about 0.12 mm, for example about 0.13 mm, such as about 0.14 mm, for example about 0.15 mm, such as about 0.16 mm, for example about 0.17 mm, such as about 0.18 mm, for example about 0.19 mm, such as about 0.20 mm, for example about 0.21 mm, such as about 0.22 mm, for example about 0.23 mm, such as 0.24 mm, for example 0.25 mm, such as 0.26 mm, for example 0.27 mm, for example about 0.28 mm, such as about 0.29 mm, for example about 0.30 mm, such as 0.31 mm, for example 0.32 mm, such as 0.33 mm, for example 0.34 mm, for example about 0.35 mm,

such as about 0.36 mm, for example about 0.37 mm, such as 0.38 mm, for example 0.39 mm, such as 0.40 mm, for example 0.42 mm, for example about 0.44 mm, such as about 0.46 mm, for example a tubular structure having an internal radius of about 0.48 mm.

36. The method of any of claims 32 to 35, wherein the flow restricting component of the shunt body comprises a single tubular structure having an internal diameter of less than 0.2 mm.

37. The method of any of claims 34 to 36, wherein the length of the at least one tubular structure of the flow restricting component of the shunt body is in the range of from about 3.0 mm to about 90 mm, such as from about 3.0 mm to about 80 mm, for example from about 3.0 mm to about 75 mm, such as from about 3.0 mm to about 70 mm, for example from about 3.0 mm to about 65 mm, such as from about 3.0 mm to about 60 mm, for example from about 3.0 mm to about 55 mm, such as from about 3.0 mm to about 50 mm, for example from about 3.0 mm to about 45 mm, such as from about 3.0 mm to about 40 mm, for example from about 3.0 mm to about 35 mm, such as from about 3.0 mm to about 30 mm, for example from about 3.0 mm to about 25 mm, such as from about 3.0 mm to about 22 mm, for example from about 3.0 mm to about 20 mm, such as from about 3.0 mm to about 18 mm, for example from about 3.0 mm to about 16 mm, such as from about 3.0 mm to about 14 mm, for example from about 3.0 mm to about 12 mm, such as from about 3.0 mm to about 10 mm, for example from about 10 mm to about 90 mm, such as from about 10 mm to about 80 mm, for example from about 10 mm to about 75 mm, such as from about 10 mm to about 70 mm, for example from about 10 mm to about 65 mm, such as from about 10 mm to about 60 mm, for example from about 10 mm to about 55 mm, such as from about 10 mm to about 50 mm, for example from about 10 mm to about 45 mm, such as from about 10 mm to about 40 mm, for example from about 10 mm to about 35 mm, such as from about 10 mm to about 30 mm, for example from about 10 mm to about 25 mm, such as from about 10 mm to about 20 mm, for example from about 10 mm to about 15 mm, such as about 10 mm, for example about 15 mm, such as about 20 mm, for example about 22 mm, such as about 24 mm, for example about 26 mm, such as about 20 mm, for example about 22 mm, such as about 24 mm, for example about 26 mm, such as

about 28 mm, for example about 30 mm, such as about 32 mm, for example about 34 mm, such as about 36 mm, for example about 38 mm, such as about 40 mm, for example about 45 mm, such as about 50 mm, for example about 55 mm, such as about 60 mm, for example about 65 mm, such as about 70 mm, for example about 75 mm, such as about 80 mm, for example about 85 mm.

38. The method of claims 36 or 37, wherein the total length of the at least one tubular structure of the flow restricting component of the shunt body is divided in two or more individual segments.

39. The method of any of the preceding claims comprising the further step(s) of connecting the sinus catheter to the shunt body at a second location thereof, and/or connecting the brain ventricle catheter to the shunt body at a first location thereof.

40. The method of any of the previous claims, wherein cerebrospinal fluid is shunted from a brain ventricle to either or both of the two large venous sinuses of the cranium that begin at the bony protuberance on the middle of the inner surface of the occipital bone at the intersection of its bony ridges and terminate at the jugular foramen on either side.

41. The method of claim 40, wherein the cerebrospinal fluid is shunted from the brain ventricle and to the sagittal sinus.

42. The method of claim 40, wherein the cerebrospinal fluid is shunted from the brain ventricle and to the transverse sinus.

43. The method of any of the previous claims, wherein the shunt body of the shunt system further comprises at least one check valve for preventing cerebrospinal fluid present in the sinus catheter or cerebrospinal fluid having been shunted to the sinus system of the individual from flowing back from the sinus catheter or from the sinus system to the shunt body or to the brain ventricle catheter.

44. The method of claim 43, wherein the at least one check valve of the shunt body does not have any inherent resistance or opening pressure, and essentially does not exert any resistance on the flow of cerebrospinal fluid from the brain

ventricle catheter through the shunt body to the sinus catheter.

45. The method of any of claims 43 and 44, wherein the resistance to flow thorugh the shunt body is independent of the at least one check valve and defined solely by the flow resistance of the flow restricting component.

46. The method of any of claims 43 to 45, wherein the operation of the at least one check valve is independent of a predetermined opening pressure to be overcome by the differential pressure defined by the difference between the intracranial pressure and the pressure in the sinus.

47. The method of any of claims 43 to 46, wherein the at least one check valve comprises a ball valve and optionally further comprises valve members selected from the group consisting of guided rigid valve members and flexible valve members, including rigid, ring shaped valve members, and flexible valve members such as tongue-shaped laminae.

48. The method of any of any of claims 43 to 47, wherein the at least one check valve comprises a mitral silicone valve.

49. The method of any of the previous claims comprising the further steps of connecting the brain ventricle catheter to a first end location of said shunt body, and connecting the sinus catheter to a second end location of said shunt body.

50. The method of any of the previous claims,

wherein the shunt system comprises
a shunt body (10) made from silicone rubber, an antechamber (11) having opposite flat walls (12) made from hard silicone rubber, and opposite domed walls (13) made from soft, perforatable, self-healing silicone rubber,

wherein at the proximal end (the top end) the chamber walls end in a tapering end comprising a tip (14), to which a brain ventricle catheter (15) can be connected and secured,

wherein the antechamber (11) is connected to the tubular flow restricting component (16) so that the distal end of the chamber (11) forms an inlet to a tubular flow restricting component (16),

wherein at least one check valve or non-return valve (17) is arranged both at the entrance to the antechamber (11) and at the outlet of the tubular flow restricting component (16),

wherein fluidic connection to the sinus of the invividual is provided by a tubular drain (18), and

wherein fluidic connection to a brain ventricle of the invividual is provided by a brain ventricle catheter (15).

51. The method of any of the previous claims, wherein the brain ventricle catheter (15) is attached to the tip or inlet connector (14), which is provided with an annular bead, and wherein the the brain ventricle catheter is optionally secured by means of a ligature.

52. The method of any of the previous claims, wherein the length of the connector (14) is about 5 mm.

53. The method of any of claims 50 to 52, wherein the tubular flow restricting com ponent (16) is dimensioned in accordance with Hagen-Poiseulle's law so as to provide a passive and substantially constant resistance to flow of less than 8 mm Hg/ml/min.

54. The method of any of claims 50 to 53, wherein the tubular flow restricting com ponent is substantially straight, and wherein the inner walls of the flow restricting component is substantially smooth.

55. The method of any of claims 50 to 54, wherein the material from which the walls of the tubular flow restricting component is made is selected from the group consisting of hard silicone rubber, HD polyethylene, such as gas sterilized poly propylene, polycarbonate, polysulfone, polystyrene, PVC and titanium.

56. The method of any of claims 50 to 55, wherein the tubular drain (18) for the sinus is made from titanium or silicone rubber.

57. The method of any of claims 50 to 56, wherein the distal 5 mm of the tubular drain (18) has an outer diameter of 2 mm and an inner diameter of 1.5 mm, and wherein the part of the drain that goes through the skull has generally an outer diameter of 3 mm and an inner diameter of 1.5 mm, and wherein the distance of the part of the drain with the largest diameter can be regulated so as to fit the distance from the shunt body to the hole over the sagittal sinus.

58. The method of any of claims 50 to 57, wherein the tubular drain (18) comprises a titanium tube with an inner diameter of 1.5 mm and a length of about 20 mm attached to a silicone rubber tube with and outer/inner diameter of 3/1.5 mm, and a length of about 60 mm.

59. The method of any of the previous claims comprising the further step of guiding the silicone rubber tube into the sinus through a borehole in the skull of the individual, wherein guidance is achieved by operating a stilet contained in the tubular drain (18).

60. The method of any of the previous claims for shunting cerebrospinal fluid, wherein the flow rate of shunted cerebrospinal fluid is constant.

61. The method of any of the previous claims for shunting cerebrospinal fluid, wherein the constant flow rate is in the range of from 40 ml per hour to 140 ml per hour.

62. The method of claim 61 for shunting cerebrospinal fluid, wherein the constant flow rate is about 40 ml per hour, such as about 45 ml/hour, for example 50 ml per hour, such as about 55 ml/hour, for example about 60 ml per hour, such as about 65 ml/hour, for example about 70 ml per hour, such as about 75 ml/hour, for example about 80 ml per hour, such as about 85 ml/hour, for example about 90 ml per hour, such as about 95 ml/hour, for example 100 ml per hour, such as about 105 ml/hour, for example about 110 ml per hour, such as

about 115 ml/hour, for example about 120 ml per hour, such as about 125 ml/hour, for example about 130 ml per hour, such as about 135 ml/hour, for example about 140 ml per hour, such as from 40 to 50 ml per hour, for example from 50 to 60 ml per hour, such as from 60 to 70 ml per hour, for example from 70 to 80 ml per hour, such as from 80 to 90 ml per hour, for example from 90 to 100 ml per hour, such as from 110 to 120 ml per hour, for example from 120 to 130 ml per hour, such as from 130 to 140 ml per hour.

63. The method of any of the previous claims for shunting cerebrospinal fluid, wherein the intercranial pressure of the individual is in the range of from -170 mm Hg to 200 mm Hg.

64. The method of any of the previous claims wherein either all or part of i) the inter nal or external surface of the shunt body, or either all or part of ii) the internal or external surface of the brain ventricle catheter, or either all or part of iii) the internal or external surface of the sinus catheter, can comprise a biocompatible and/or hemocompatible material comprising an inert surface preventing biological material from maintaining contact with the inert surface, and/or comprising a hemocompatible surface coated with a plurality of charged species capable of increasing the hemocompatibility of the surface.

65. The method of claim 64, wherein said biocompatible and/or hemocompatible material is carbon-based.

66. The method of claim 64 wherein said carbon-based biocompatble and/or hemocompatible material comprises or consists of Diamond-Like Carbon (DLC).

67. The method of claim 64 wherein said carbon-based biocompatible and/or hemocompatible material comprises or consists of a turbostratic carbon.

68. The method of claim 64 wherein wherein said carbon-based biocompatible and/or hemocompatible material comprises or consists of a pyrolytic carbon.

69. The method of claim 64 wherein said biocompatible/hemocompatible material comprises or consists of a Sputtered carbon.

70. The method of claim 64, wherein said biocompatible/hemocompatible material comprises or consists of Graphit-iC

71. The method of claim 64, wherein said biocompatible/hemocompatible material comprises or consists of Teflon.

72. The method of claim 64, wherein said biocompatible/hemocompatible material comprises or consists of a Ceramic

73. The method of claim 72, wherein said biocompatible/hemocompatible material comprises or consists of titanium nitride (TiN)

74. The method of claim 64, wherein said biocompatible/hemocompatible material is Phosphatidyl choline di-ester.

75. Use of a shunt body comprising a flow restricting component capable of maintaining a passive and essentially constant resistance to outflow of CSF through the shunt body, in the manufacture of a shunt system for shunting toxic substances present in brain tissue and/or the CSF space to the sinus system of an individual suffering from, or at risk of developing, a condition related to the retention and/or accumulation of toxic substances in brain tissue and/or the CSF space.

76. The use according to claim 75, wherein said condition is according to any of claims 2-8.

77. The use according to any of claims 75-76, wherein said shunt system is according to any of claims 10-38, 43-48, 50-58, 64-74.